

CLAIMS

We claim:

1. A dosage form providing a higher concentration of Active Pharmaceutical Ingredient using solid free form fabrication to form successive layers of a powder and a dispensed binder fluid into a three-dimensional matrix dosage form, comprising:

a porous or solid matrix; and

an Active Pharmaceutical Ingredient selectively distributed within the matrix of the dosage form, the Active Pharmaceutical Ingredient substantially insoluble in water, ethanol, methanol and chloroform, wherein the Active Pharmaceutical Ingredient is in an amorphous state.

2. ¹¹² The dosage form of claim 1 wherein the method is three-dimensional printing, comprising depositing a layer of powder and applying a suspension dispensed onto the powder, the suspension including solid particles wherein the solid particles include at least one of an Active Pharmaceutical Ingredient and are in the range of greater than or equal to 20-wt% to less than or equal to 50-wt% of the suspension.

3. The dosage form of claim 2 wherein the solid particles are greater than or equal to 100 nanometers in size and are less than or equal to 5 microns in size.

4. The dosage form of claim 2 wherein the solid particles include more than one Active Pharmaceutical Ingredient.

5. The dosage form of claim 2 wherein the suspension has a viscosity of less than or equal to 20cP and greater than or equal to 0.3cP.

6. The dosage form of claim 2 further comprising, an additive in the suspension to prevent agglomeration of the solid particles.

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7. The dosage form of claim 6 wherein the additive is a steric hindrant.
8. The dosage form of claim 2 further comprising, a surfactant in the suspension to change a surface charge of the solid particles.
9. The dosage form of claim 2 wherein the Active Pharmaceutical Ingredient is a drug selected from the group consisting of ibuprofen, nitrofurantoin, acetaminophen, ondansetron, taxol, lovastatin, ciprofloxacin hydrochloride, and sulfonamide (sulfamethoxazole).
10. The dosage form of claim 2 wherein at least some of the solid particles are soluble or partially soluble and are present in concentrations above a saturation level for the solid particle.
11. A method of manufacturing a dosage form, comprising:
depositing a layer of excipient powder;
dispensing a suspension comprising solid particles of at least one Active Pharmaceutical Ingredient onto portions of the layer of excipient powder;
and repeating the above steps as many times as needed to produce the dosage form.
12. The method of claim 11 wherein the dispensing is done by a microvalve-based dispenser.
13. The method of claim 12 wherein the concentration of suspended solid particles in the dispensed liquid is less than 5-wt%.
14. The method of claim 12 wherein the dispensing further includes opening and closing the valve repeatedly.

15. The method of claim 12 wherein the dispensing comprises opening the valve and leaving it open for as long as needed to print a particular region.

16. The method of claim 11 further including, continuously circulating the suspension through a fluid supply system.

17. The method of claim 11 wherein the dispensing is done by a continuous-jet dispenser.

18. The method of claim 17 wherein the concentration of suspended solid particles in the dispensed liquid is larger than 20-wt%.

19. The method of claim 11, wherein the suspension further comprises suspending agents and/or steric hindrants.

20. The method of claim 11, wherein the suspension further comprises one or more additional Active Pharmaceutical Ingredients dissolved in the liquid.

21. The method of claim 11, wherein the suspension further comprises one or more binding substances dissolved in the liquid.

22. The method of claim 11, wherein the solid particles have all dimensions less than or equal to 5 microns.

23. The method of claim 11 wherein the solid particles are in the dimensional range of less than or equal to 5 microns and greater than or equal to 100 nanometers.

24. The method of claim 11, further comprising dispensing a non-suspension binder liquid onto portions of the layer of excipient powder in a pattern of places different from where the suspension is dispensed.

25. The method of claim 11, further comprising, after dispensing, allowing or causing the dispensed suspension to at least partially dry, and dispensing a second suspension containing solid particles of at least one Active Pharmaceutical Ingredient again onto portions of the layer of excipient powder, at least one additional time before depositing the next layer of excipient powder.

26. The method of claim 25 wherein the pattern of deposition during the second printing is different from the pattern during the first printing.

27. The method of claim 11, wherein at least some of the suspended solid particles comprise an amorphous form of Active Pharmaceutical Ingredient.

28. A dosage form comprising:

a powder excipient; and

an Active Pharmaceutical Ingredient that is substantially insoluble in water, ethanol, methanol and chloroform, the Active Pharmaceutical Ingredient is in an amorphous state, the Active Pharmaceutical Ingredient having a local concentration at local places in the dosage form, wherein the local concentration of API is nonuniform.

29. The dosage form of claim 28 wherein the dosage form contains a gradient in the concentration of API.

30. The dosage form of claim 28 wherein the concentration of API is approximately zero in some places.

31. The dosage form of claim 28 wherein the places of approximately zero concentration of API form an enclosure around places having a non-zero concentration of API.

32. A dosage form comprising:
an excipient in the form of a powder; and

an API having a respective solubility at room temperature in water, ethanol, methanol and chloroform, and having a largest solubility which is the largest of those respective solubilities, wherein the dosage form has an overall dosage form volume, wherein the total content of API in the dosage form is more than three times the overall dosage form volume multiplied by the largest solubility; the API having a local concentration at local places in the dosage form, and wherein the local concentration is nonuniform.

33. The dosage form of claim 32 wherein the local concentration of API is greater than 50 mg/cc.

34. The dosage form of claim 32 wherein the dosage form contains a gradient in the concentration of API.

35. The dosage form of claim 32 wherein some regions of the dosage form contain an approximately zero concentration of API.

36. The dosage form of claim 32 wherein the places of approximately zero concentration of API form an enclosure around places having a non-zero concentration of API.

37. A dosage form manufactured by the method of claim 11.

38. A method of manufacturing a biomedical article, comprising:
depositing a layer of powder;

dispensing, onto portions of the layer of powder, a suspension comprising solid particles of at least one substance selected from the group consisting of: cells, cell fragments, cellular material, proteins, growth factors, bone particles, cartilage particles, other biological or inert materials which are insoluble or nearly insoluble, Active Pharmaceutical Ingredients, and very fine particles of the same material as the powder in the layer of powder;

and repeating the above steps as many times as needed to produce the biomedical article.

39. The method of claim 38 wherein the suspension further comprises suspending agents and/or steric hindrants.

40. The method of claim 38 wherein the suspension further comprises one or more additional API dissolved in the liquid.

41. The method of claim 38 wherein the suspension further comprises one or more binding substances dissolved in the liquid.

42. The method of claim 38 wherein the biomedical article is an implantable device.

43. The method of claim 38 wherein the biomedical article is a bone substitute.

44. The method of claim 38, further comprising, after dispensing, allowing or causing the dispensed suspension to at least partially dry, and dispensing a second suspension containing solid particles of at least one Active Pharmaceutical Ingredient again onto portions of the layer of excipient powder, at least one additional time before depositing the next layer of excipient powder.

45. The method of claim 44 wherein the pattern of deposition during the second printing is different from the pattern during the first printing.

46. The method of claim 38, wherein at least some of the suspended solid particles comprise an amorphous form of Active Pharmaceutical Ingredient.

47. The biomedical article of ¹¹²claim 44 wherein the second substance has a local concentration at local places in the dosage form and wherein the local concentration of the second substance is nonuniform.

48. A biomedical article manufactured by the method of claim 38.

49. A biomedical article comprising:

a powder which is substantially insoluble;

a second substance selected from the group consisting of: cells, cell fragments, cellular material, proteins, growth factors, bone particles, cartilage particles, other biological or inert materials which are insoluble or nearly insoluble, Active Pharmaceutical Ingredients, and very fine particles of the same material as the powder in the layer of powder.

50. A. method of three-dimensional printing, comprising dispensing a suspension through a solenoid-operated valve onto powder.

51. The ¹¹²method of claim 49 wherein the valve includes a valve body and within the valve body a seat and a moving part, and a bypass flowpath.

52. The ¹¹²method of claim 49 further comprising flowing suspension continuously through a manifold, and wherein the microvalve is supplied from the manifold.

53. A solenoid-operated valve having a valve body and within the valve body a seat and a moving part adapted to fit against the seat and thereby close a flowpath, and further comprising a bypass path emanating from the valve body close to the valve seat, the bypass path being always open.